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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,784	12/08/2005	Mitsuko Kosaka	64603(70904)	8189

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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,784	KOSAKA, MITSUKO	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-14* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 November 2009 has been entered.

Status of Application, Amendments and/or Claims

2. The amendment filed on 12 November 2009 has been entered into the record and has been fully considered.

3. Claim 7 is amended.

4. Claims 1-6, 11-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

5. Claims 7-8, drawn to a method for producing rhodopsin-positive retinal nerve cells by isolating and differentiating iris pigmented epithelial cells in a serum free culture medium, are being considered for examination in the instant application.

Withdrawn objections and/or rejections

6. Upon consideration of the Applicant's amendment to introduce the "rhodopsin-positive" limitation in independent claim 7, the rejection under 35 U.S.C. 103(a) has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 7-8, are rejected under 35 U.S.C. 103(a) as being unpatentable over Haruta et al., (Nat Neurosc 4: 1163-1164, 2001), in view of Tropepe et al. (Sc. 287: 2032-2036, 2000) and in further view of Kosaka et al. (Exp Cell Res 245: 245-251, 1998).

8. The claims are drawn to a method for producing rhodopsin-positive retinal nerve cells by isolating and differentiating iris pigmented epithelial (IPE) cells derived from a bird or a mammal, wherein the differentiation is induced by adherent culturing in a serum-free culture medium containing one of FGF2, FGF9 and CNTF at a concentration of 1-100 ng/ml, and wherein the IPE cells are not subjected to gene transfer. The claims also recite that the density of IPE cells in the medium at the start of the adherent culture is 1×10^5 cells/cm^2 or less.

Please note that based upon teachings in the instant specification and Reynolds reference cited therein, the differentiation to retinal nerve cells without gene transfer in IPE cells can encompass conventional processes like selective culturing step producing spheres by floated coagulated mass culturing technique (page 9, para 3; pages 25-26, Second Embodiment; page 14, para 1; Figures 1, 3 (steps S1, S2 and S12)).

9. Haruta et al. teach the plating and maintenance of iris tissue from adult rats in serum free culture medium containing bFGF or FGF2, resulting in the proliferation of cells as a monolayer (Figure 1a, page 1163, para 2), wherein the iris derived cells are positive for a retinal ganglion cell marker, neurofilament 200. Haruta et al. further teach that ciliary margin cells can differentiate to rod photoreceptors (that would inherently be rhodopsin positive) **subsequent to formation of spherical colonies** (page 1163, col 2, para 4), and suggest that **iris derived cells can be cultured to obtain spheres or spherical colonies to induce differentiation to rod photoreceptors without gene transfer** (emphasis added) (page 1164, col 1, para 1), because the iris and ciliary derived cells can behave similarly under similar culture conditions (page 1164, col 1, para 1).

10. Although Haruta et al. do not teach spherical colonies, the technique of making and using spherical colonies for various cell types including pigmented cells from the ciliary margin and retina, in coagulated mass cultures was well established. Tropepe et al teach the proliferation of pigmented cells from the

ciliary margin (PCM) obtained from adult mouse eyes using the in vitro spherical colony forming culture method, that results in cells that are multipotential (page 2034, col 1, para 2). It is well established that this method is used for culture and differentiation without gene transfer (see instant specification page 9, para 3), wherein the selective culturing by floated coagulated mass can be used for obtaining and selecting specific cell types.

11. Haruta et al and Tropepe et al. do not provide the specifics of the culture medium.

12. Kosaka et al. teach the isolation of iris pigmented epithelial cells (IPE) from chicken eyeballs in Eagle's MEM (page 246, column 1, "Preparation of cell"). Kosaka et al. further teach that the IPE cells are depigmented and seeded for transdifferentiation to lens tissue cells at a cellular density of 0.5-1 x 10^4 cells/cm^2 using monolayer cell culture (page 246, col 1, para 1-3). The reference also teaches that basic fibroblast growth factor (bFGF) or FGF2 in the culture medium at a concentration of 1-30 ng/ml, promote growth and differentiation of IPE cells (page 248, Figure 4).

13. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of culturing iris derived cells without gene transfer by using selective culturing and forming spherical colonies in serum free culture medium and FGF2 for the differentiation to photoreceptors in view of Haruta et al. and Tropepe et al., by using Eagle's medium as taught by Kosaka et al. The person of ordinary skill in the art would

have been motivated because IPE and the neural retina have a common developmental origin, thereby giving rise to retinal neurons (Haruta et al. page 1163), and that cells of the retinal pigmented epithelium and IPE perform similar functions in the appropriate environment. Furthermore, a person of ordinary skill in the art would be motivated to use serum-free culture medium because serum is known to contain a mixture of various constituents including different growth factors that would induce differentiation to a non-specific mixture of cells, as opposed to a directed differentiation to retinal nerve cells using specific growth factors at specific concentration, as required by the instant claims. The person of ordinary skill in the art would have expected success because the method of adherent cell culture in serum free medium for differentiation of stem cells and differentiation induction without gene transfer, was well established and accepted in the art at the time the invention was made.

14. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Applicant's Remarks

15. Although the earlier rejections under 35 USC 103 has been withdrawn, and new rejections necessitated by the current claim amendments have been submitted in the current Office Action, the same references as used in the previous Office Action have been cited for the new rejections. Applicant's

remarks directed to the citations and those that stay relevant to the new rejections will be responded herein.

16. Applicant's arguments are essentially directed to the new limitation "rhodopsin-positive", asserting that Haruta et al do not teach that the cells express the rhodopsin marker for rod photoreceptors. Applicant also argues that "regardless of the fact that IPE cells and retinal nerve cells have a common developmental origin", a person of ordinary skill would not predict that IPE cells could differentiate to rhodopsin-positive cells at the time of filing of the present application. Applicant provides a treatise by the inventors in support of this contention.

17. Applicant's arguments are fully considered, however, are not found to be persuasive. Although agreed that Haruta et al. teach that only IPE cells transfected with the retinal homeobox Crx gene specific for photoreceptors, differentiate to rod photoreceptors in monolayer cell culture, Haruta et al also suggest that IPE cells forming spherical colonies could give rise to photoreceptors. Because the technique of inducing differentiation by floated coagulated mass and formation of spherical colonies without gene transfer was well known in the art at the time of filing of the instant invention, the person of ordinary skill would certainly be motivated to try using this culture technique based upon explicit suggestion of Haruta et al.

18. Applicant's arguments with regards to the treatise is irrelevant, particularly

because the differentiation conditions are different, e.g. the treatise does not teach the use of spherical colony formation for differentiation. Moreover the treatise emphasizes that the “growth factors and extracellular matrix components" are important in the transdifferentiation or differentiation of pigmented epithelial cells of vertebrates (Amemiya et al. Biochem Biophys Res Comm 316:1-5, 2004; page 3, col 1, para 2).

19. Because ciliary epithelial and IPE cells are all ectodermic cells having a common developmental origin, the artisan would have immediately recognized that techniques that work on one set of cells from this origin would be likely to work on other cell types from the same developmental lineage. Therefore, absent evidence to the contrary, the technique of using spheres under similar culture conditions for retinal photoreceptor cell differentiation, would be obvious to one skilled in the art in view of Haruta et al. and Tropepe et al. Furthermore, such knowledge would lead to a reasonable expectation of success. It is noted that in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom (*In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968)).

Also, a reference must be considered, under 35 U.S.C. 103, not only for what it expressly teaches but also for what it fairly suggests; all disclosures of prior art, including unpreferred embodiments, must be considered in determining obviousness (*In re Burckel* 201 USPQ 67 (CCPA 1979)).

20. Based on the above reasoning, the combined teachings of Haruta et al, Topepe et al and Kosaka et al. render the inventive method obvious and predictable to the person of ordinary skill in the art.

Conclusion

21. No claims are allowed.

22. This is a RCE of applicant's earlier Application No. 10/559,784. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

23. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is 571-272-9037. The examiner can normally be reached on M-F.

25. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Stucker, can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

26. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
12 February 2010

/Daniel E. Kolker/

Primary Examiner, Art Unit 1649

February 28, 2010